The Roles of Laparoscopy in Treating Ovarian Cancer

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SUMMARY

Great advances in technology offer meticulous options of minimally invasive surgery to empower the gynecologists to manage patients of early ovarian cancer. Laparoscopy affords improved visualization of the pelvic peritoneum, diaphragm and the deep pelvic structures, and offers many advantages in the avoidance of long abdominal incision, including shorter hospital stay and a more rapid recovery time. Most studies showed that laparoscopy did not compromise the survival and recurrence prognosis in comparison with open abdominal approach of staging surgery. Contrarily, laparoscopy precludes the advantage of open surgery, such as manual examination of the full extent of the bowel and palpation of lymph nodes. Besides, laparoscopy technically hampers the removal of large ovarian mass, and laparoscopic cancer surgery has a potential risk of trocar site metastasis. As the trend shows that laparoscopy has been playing an important role in treating early ovarian cancer, we could expect laparoscopy to become an attractive surgical option in the future for ovarian cancers. [*Taiwan J Obstet Gynecol* 2009;48(1):9–14]

Key Words: laparoscopy, ovarian cancer, port site metastasis, unexpected malignancies

Introduction

Laparoscopy offers many advantages including avoidance of an abdominal incision, shorter hospital stay, and a more rapid recovery time. Large case series have documented the safety and efficacy of laparoscopic removal of adnexal masses. A study involving removing suspicious adnexal masses from 138 patients reported a mean operation time of 86 minutes (range, 25–210 minutes), a mean hospital stay of 1.5 days, and the major intraoperative complications rate at 1.4%, which were all favorable in comparison with those by laparotomy [1]. Laparoscopy has also been shown to be feasible with large adnexal masses greater than 10 cm [2]. Thus, laparoscopy is a viable option when approaching simple or complex, and large or small adnexal masses.

However, unexpected malignancies could be inevitably encountered in laparoscopic adnexal surgeries. Ovarian cancer remains the leading cause of fatality among all gynecologic cancers. The American Cancer Society estimates that the case number of newly diagnosed ovarian cancer in the United States for 2008 was 21,650 and ranked the eighth highest among cancers in women. However, the expected number of deaths from ovarian cancers was 15,520 and ranked the fifth highest, and this number is much higher than the expected number of 7,470 of uterine corpus cancer, which was ranked the eighth highest [3]. In the 26th Annual Report of the Federation of International of Gynecologists and Obstetricians (FIGO), the 5-year survival rate for stage IA–IC ovarian cancer was 83.4–89.6% [4].

No matter whether the approach is laparotomy or laparoscopy, guidelines for the treatment of patients with early-stage ovarian cancer include total hysterectomy, bilateral salpingo-oophorectomy, bilateral

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pelvic/paraaortic lymphadenectomy, omentectomy, and multiple intra-abdominal biopsies in stage I ovarian cancer. Many surgeons consider laparoscopy to be a safe and feasible approach for assessment and removal of early ovarian cancer [5–12].

Thoughtful considerations will ensure that the patient benefits from the laparoscopic surgery while avoiding the undue morbidity and without compromising the long-term survival. Key points in ovarian cancer treatment include the indication and feasibility of the laparoscopic surgery for cancer, the cost and benefit of laparoscopy in ovarian cancer for the patients and surgeons, and the survival and recurrent outcome of the treatment. These are discussed as follows.

Unexpected Malignancies Encountered in Laparoscopy

The difficulties to diagnose an early adnexal cancer preoperatively are: the vague and polymorphic presentation in its early stage, the lack of a convincible diagnostic criteria, and the low prevalence of ovarian cancer in the general population (about 30–50 cases per 100,000 women) [13,14]. Few series of laparoscopic management of unexpected ovarian malignancies have been published in the literature. In a series of 1,011 patients operated by laparoscopy, four ovarian cancers were revealed intraoperatively in 1,209 adnexal masses ranging from 2 cm to 25 cm in size [12], and an Austrian survey found an incidence of 6.5 unexpected ovarian cancer in 1,000 women with adnexal mass managed by laparoscopy [15]. Another French survey found 78 cases of malignant ovarian cysts out of 5,307 ovarian lesions treated by laparoscopy (1.47%), in which 18 of the 78 cases (0.34%) were ovarian cancers and the remaining 60 were borderline tumors [16]. A recent review concluded that the unexpected ovarian malignancy was estimated to be 1% or less in premenopausal patients under strict selection criteria; however, in postmenopausal patients, this rate rises to 3.0% [17]. Therefore, the rate of unexpected malignancies depends mostly on the selection criteria used.

Does Rupture or Spill from the Cyst Matter?

A concern of laparoscopic cancer surgery is cyst rupture and tumor spillage during operation, which may result in potential unfavorable sequelae and affect the overall survival. The rate of cyst rupture in laparoscopy has been reported as 6–27%, which is supposed to be higher than laparotomy as a risk of tumor spillage, although the data are not conclusive [18–21].

An earlier study indicated that a ruptured cyst was associated with a reduced 5-year survival in stage I epithelial ovarian cancer [22]. However, subsequent studies have shown that intraoperative cyst rupture is not associated with reduced survival. Some authors showed that there was a statistically significant reduction in survival in the group whose cyst ruptured before surgery compared with the group with intraoperative cyst rupture [23–26]. A recent retrospective analysis of 1,545 patients with stage I disease found that intraoperative cyst rupture had an independent unfavorable prognostic effect on disease-free survival (hazard ratio, 1.64; 95% confidence interval, 1.07–2.51; $p = 0.002$) [27].

Feasibility of the Cancer Laparoscopy

A review of 24 patients with ovarian cancer FIGO stage IA–B underwent laparoscopic surgery for either primary treatment (13/24) or completion of staging (11/24) after a mean of 12 days (range, 4–21 days) after primary surgery reported a favorable outcome. Mean operative time was 166 minutes (range, 118–206 minutes) for completion of staging and 182 minutes (range, 141–246 minutes) for primary surgery. No major intraoperative complication and no trocar metastasis occurred. Five of the 24 patients (20.8%) received adjuvant chemotherapy after a median time of 7 days (mean, 5–14 days) following surgery, and two of the 24 patients (8.3%) developed recurrence. After a median follow-up of 46 months, disease-free survival was 91.6% and overall survival 100% [9]. In another review of 160 patients at high or low risk for ovarian malignancy who underwent laparoscopic removal of an adnexal mass, the major and minor postoperative complication rates were 2% and 4%, respectively [28].

Does Pneumoperitoneum Cause the Acceleration of Spread of Malignant Cells?

Several studies have compared tumor growth after laparotomy and after pneumoperitoneum in animal models, and most of them found a greater tumor growth after laparotomy [29–32]. Some experiments suggested that the carbon dioxide in the pneumoperitoneum environment may have a growth-stimulating effect on tumor cells [33–35].

Port Site Metastasis

The occurrence of intraperitoneally cancerous dissemination and/or abdominal wound (port site) metastases after laparoscopic procedures has been reported by numerous authors [1,36–51]. The incidence of port site metastasis has been reported to range from 0% to 16% in a variety of cancers, which seemed no higher than that with laparotomy. However, port site metastasis could be an isolated occurrence or as part of a disseminated state, and the presentation of a port site metastasis after cancer laparoscopy varies from a few days to several years. Prognosis of patients with port site metastasis after cancer laparoscopy varies widely according to sites of origin and histology.

Establishment of port site metastasis needs the presence of seeds and appropriate soil. Various possible mechanisms have been postulated as the cause of port site recurrence, such as advanced malignancy, direct contamination of cancer cells following extensively unprotected manipulation or presence of ascites, gas leak around port sites in the pressure of pneumoperitoneum (chimney effect), and tissue acidosis in the use of carbon dioxide. Increased traumatic injuries at the port site or predilection of tumor cell growth in the subcutaneous tissue may facilitate such process, since borderline malignant tumors can harbor sole abdominal wall implants without poor outcome. Some procedures to minimize the risk of port site implants have been recommended, including: (1) using wound protectors; (2) minimizing tumor manipulation; (3) anchoring ports to prevent dislodgment; (4) avoiding carbon dioxide leakage and sudden desufflations; (5) using gasless laparoscopy; (6) irrigating and suctioning abdomen, instruments and ports before removal; (7) using heparin or 0.25–1% povidone-iodine solution to irrigate wounds and abdomen; (8) excising trocar sites and with deliberate closure of all abdominal layers including the peritoneum after laparoscopy; or postoperative port site radiation; (9) resuming to definitive surgery or chemotherapy early; and (10) using 5-fluorouracil, topical taurolidine or intraperitoneal endotoxin. Despite the vast amount of literature on this issue, solid evidence, however, is lacking on the effectiveness of prevention or management [52,53].

For ovarian malignancy, the real incidence of port site metastasis is not known, but there have been 44 cases reported in the English language literature [9,54,55]. In an earlier study of patients of ovarian cancer in stage III and IV exclusively, six deaths were noted in seven (86%) who had abdominal wall metastases as compared with 63 deaths in 137 (46%) who had no wound tumors [43]. However, the difference did not achieve significance because of the small sample size. Another study reported that by defining the breakpoint at 17 days, the prolonged interval of staging laparotomy after initial laparoscopic surgery was an independent prognostic factor for the stage of disease [47]. A later series also found a significant correlation between the development of port site implants and the longer interval before the start of chemotherapy or cytoreductive surgery; however, this study concluded that the presence of port site implants ($n=9$) did not significantly impact the outcome [48]. Generally, most of the reports involved small case numbers and limited follow-up periods; the true incidence, mechanism, and long-term prognosis of these patients are still unclear.

We have found in our previous study that some biomarkers may be useful to predict the prognosis [56]. Patients who developed port site metastasis in our series were relatively young and without stage IA tumor, and had higher synthetic phase fraction than those without port site metastasis (18.2% *vs.* 9.9%; $p=0.003$; relative risk ratio [$>15.5\%$ *vs.* $\leq 15.5\%$], 38.33; 95% confidence interval, 3.3–449.2). Two patients were currently alive then without disease, and their tumors were p27-positive, and p53-, HER-2/neu- and bcl-2-negative [56]. We found that hematogenous spread could be one of the possible mechanisms of port site metastasis, as we noted that two patients who presented with isolated port site recurrence developed lung recurrence at a period after chemotherapy and a complete remission of port site metastasis [56].

We also established a nude mouse model of laparoscopy to evaluate the influence of intraperitoneal chemotherapy with paclitaxel on the prevention of intraoperative cancer scattering during laparoscopy and on the efficacy in reducing trocar site metastasis. We found that total tumor weights were closely correlated with ascites vascular endothelial growth factor (VEGF) concentrations in a positive exponential relationship, and paclitaxel is a drug of choice because of not only its cytotoxic effect but also its significant anti-VEGF ability that can block the cycle of reciprocal stimulation of ovarian cancer growth and VEGF secretion, which can result in an inhibition of both angiogenesis and cancer cell proliferation [57]. Besides, tumor implantation and port site metastases were reduced more by the intraoperative intraperitoneal administration of paclitaxel during the operation than by administration after the operation. Thus, intraoperative intraperitoneal administration of paclitaxel may decrease significantly the occurrence of port site

metastasis and intraperitoneal dissemination in an animal study [6,58].

Conclusion

As early-stage ovarian cancer is rarely diagnosed preoperatively, most are encountered incidentally during laparoscopic operation for benign adnexal mass. In the past, laparo-conversion was recommended to ensure an optimal staging and to avoid uncertain tumor cell spread. However, recent advancement in technology offers more meticulous options of minimally invasive surgery to empower the gynecologists to manage patients of early ovarian cancer. Patients with early ovarian cancer undergoing laparoscopic surgery could not only achieve a same or even better surgical prognosis as compared those undergoing conventional laparotomy [6,9], but also benefit from a less traumatic surgery and a potentially faster recovery, so that the patients could begin with the adjuvant chemotherapy earlier, if needed.

Some disadvantages of laparoscopic surgery for ovarian cancer could exist and should be considered before the operation, including the difficulty to remove large ovarian mass, inability to examine the lymph nodes by palpation and the full extent of bowels manually, potential risk of cancer dissemination due to intraoperative manipulation, and possible trocar site metastasis. However, some techniques can be applied to any suspicious adnexal mass even without a preoperative diagnosis of ovarian cancer, such as excising the whole mass without fragmentation, removing it with cellophane bag as carefully as possible, and sending for an immediate frozen section examination.

Note that intact surgical specimens and the use of a plastic retrieval bag do not preclude the occurrence of port site implants. If ovarian malignancy is diagnosed during the operation, adequate irrigation of povidone-iodine solution and deliberate closure of the peritoneum and all layers of abdominal wall at port site should be performed, whether the surgery was converted to laparotomy for comprehensive staging or not. If ovarian malignancy is diagnosed days after laparoscopy, standard cytoreductive surgery including excision of all port sites should be performed, and followed by chemotherapy with or without port site irradiation as soon as possible.

Laparoscopy has played an important role in treating early ovarian cancer. Although there are still some problems and difficulties to overcome in treating advanced ovarian cancers, laparoscopic management of ovarian cancers could potentially become a trend and an attractive surgical option in the near future.

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